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The toxicity of very prolonged courses of PEGasparaginase or *Erwinia* asparaginase in relation to asparaginase activity, with a special focus on dyslipidemia

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ABSTRACT

We prospectively studied the incidence and clinical course of hypertriglyceridemia and hypercholesterolemia during very prolonged use of asparaginase in relation to levels of asparaginase activity in children with acute lymphoblastic leukemia. We also evaluated the incidence of pancreatitis, thrombosis, hyperammonemia and central neurotoxicity and their association with asparaginase activity levels. Eighty-nine patients were treated according to the Dutch Childhood Oncology Group Acute Lymphoblastic Leukemia 10 medium-risk intensification protocol, which includes 15 doses of PEGasparaginase (2,500 IU/m^2) over 30 weeks. *Erwinia* asparaginase (20,000 IU/m^2) was administered when allergy to or silent inactivation of PEGasparaginase occurred. Triglyceride, cholesterol and ammonia levels increased rapidly in children treated with PEGasparaginase and remained temporarily elevated, but normalized after administration of the last asparaginase dose. Among the patients treated with PEGasparaginase, hypertriglyceridemia and hypercholesterolemia (grade 3/4) were found in 47% and 25%, respectively. The correlation between PEGasparaginase activity levels and triglyceride levels was strongest at week 5 (Spearman correlation coefficient=0.36, P=0.005). The triglyceride levels were higher in children ≥10 years old than in younger patients (<10 years old) after adjustment for type of asparaginase preparation: median 4.9 mmol/L *versus* 1.6 mmol/L (P<0.001). In patients receiving *Erwinia* asparaginase, triglyceride levels increased in the first weeks as well, but no grade 3/4 dyslipidemia was found. Hyperammonemia (grade 3/4) was only found in patients treated with *Erwinia* asparaginase (9%). Thrombosis occurred in 4.5%, pancreatitis in 7%, and central neurotoxicity in 9% of patients using either of the two agents; these toxicities were not related to levels of asparaginase activity or to triglyceride levels. In conclusion, severe dyslipidemia occurred frequently, but was temporary and was not associated with relevant clinical events and should not, therefore, be considered a reason for modifying asparaginase treatment. Dyslipidemia was the only toxicity related to levels of asparaginase activity.

Introduction

Asparaginase is a key component of the treatment of acute lymphoblastic leukemia (ALL). Many studies have shown that intensification of asparaginase treatment is essential to improve event-free survival of children with ALL.[1-5] However, the use of asparaginase is associated with multiple toxicities including thrombosis, pancreatitis, hyperammonemia, central neurotoxicity and, relatively commonly, hypertriglyceridemia and hypercholesterolemia (dyslipidemia). Although these are well-known side effects, the incidence and natural course of dyslipidemia during very prolonged treatment with PEGasparaginase or *Erwinia* asparaginase are unknown. It is also unclear whether asparaginase therapy should be interrupted or stopped if these toxic effects occur and whether the different toxicities are related to levels of asparaginase activity.

We, therefore, analyzed the incidence of dyslipidemia and its natural course during very prolonged courses of PEGasparaginase or *Erwinia* asparaginase in children with ALL. We also prospectively studied other asparaginase-associated toxicities, such as pancreatitis, hyperammonemia, thrombosis and central neurotoxicity, and their relationship to asparaginase activity.

Methods

Patients and the ALL-10 treatment protocol

From July 2009 untill October 2012, ALL-10 medium-risk patients from two pediatric oncology centers (Rotterdam and Groningen, the Netherlands) were entered into this study. The Institutional Review Board approved this study before the patients were enrolled. Informed consent was obtained from parents or their guardians and from patients ≥12 years of age. This study was conducted in accordance with the Declaration of Helsinki.

All patients received eight doses of native *E.coli* asparaginase (5,000 IU/m^2 per dose) every 3 days in induction. The intensification/continuation phase of the ALL-10 medium-risk treatment included PEGasparaginase as the first-line agent (2,500 IU/m^2 per dose) every 2

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weeks for a total of 15 doses (*Online Supplementary Figure S1*). In case of an allergy to or silent inactivation of PEGasparaginase, the patient was switched to *Erwinia* asparaginase as the second-line agent (20,000 IU/m^2 per dose) 2-3 times per week to complete 30 weeks of asparaginase therapy. In the case of high asparaginase activity levels (72 hours ≥100 U/L), the frequency of *Erwinia* asparaginase infusions was reduced to twice weekly.[6] Both asparaginase preparations were administered intravenously over 1 hour.

Study design and definitions

For practical reasons, the measurements of triglyceride, total cholesterol, and ammonia were non-fasting. Blood samples were taken at week 1 (baseline), weeks 3, 5, 7, 9, 15 and 25 during the intensification phase including asparaginase and week 37, 8 weeks after the final PEGasparaginase or 6 weeks after the final *Erwinia* asparaginase infusion.

Hypertriglyceridemia, hypercholesterolemia, hyperammonemia, pancreatitis, thrombosis and central neurotoxicity were graded prospectively according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Cholesterol levels were designated grade 3 if they were between 10.34-12.92 mmol/L and grade 4 if they were greater than 12.92 mmol/L. Triglyceride levels were defined as grade 3 if they were between five to ten times the upper limit of normal (1.0 mmol/L) and grade 4 if they were more than ten times higher than the upper limit of normal. Thrombosis was scored only if it was not related to a central venous line. To study the relation between ammonia level and central neurotoxicity, we prospectively collected central neurotoxicity items on structured case record forms assessed by the pediatric oncologists. These items were ataxia, somnolence or depressed level of consciousness, mood alteration and seizures. Central neurotoxicity included posterior reversible encephalopathy syndrome which was not mentioned in the CTCAE.

Allergy was also graded according to the NCI CTCAE version 3.0. Definitions of silent inactivation of PEGasparaginase and *Erwinia* asparaginase were previously described.[6] In total 22 patients were switched to *Erwinia* asparaginase to complete 30 weeks of asparaginase therapy; two patients had an allergic reaction to the first PEGasparaginase dose and 18 patients showed an allergic reaction to the second dose, all these patients were switched to *Erwinia* asparaginase. The remaining two patients had silent inactivation of PEGasparaginase which was detected in real-time and were switched to *Erwinia* asparaginase after the second PEGasparaginase dose.

Laboratory measurements

Asparaginase activity levels were processed and assessed as described earlier.[7] Triglyceride, cholesterol, and ammonia levels were analyzed in both medical centers. Samples for ammonia levels were put in an ice bath and were immediately processed at the laboratory.

Statistical analysis

The data were analyzed with the software packages SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 5.01 (GraphPad Prism Inc., San Diego, CA, USA).

Changes of triglyceride, cholesterol, and ammonia levels over time were evaluated using mixed models analysis of variance (ANOVA). Changes related to age and gender were also investigated using mixed models ANOVA. All analyses were done after log-transformation of measured values to get approximate normal distributions. Mean values were estimated by backtransforming the mean of log-values.

The incidence of toxicities (pancreatitis, thrombosis, central neurotoxicity) related to treatment (PEGasparaginase or *Erwinia* asparaginase) was investigated with Fisher exact tests. Spearman correlation coefficients were used to evaluate the relations between triglyceride, cholesterol and asparaginase activity levels. A two-sided P-value < 0.05 was considered statistically significant. Data are presented as mean ± standard error of the mean (SEM) or specified otherwise.

Results

Characteristics and toxicity of asparaginase preparations

We enrolled 89 patients (49% boys). The median age was 4.9 years (range, 1.2-16.2 years), 78 (88%) patients had precursor B-ALL and 11 (12%) patients had T-ALL. Twenty-two out of 89 (25%) patients were switched to *Erwinia* asparaginase because of either allergy to or silent inactivation of PEGasparaginase.

Table 1 summarizes the toxicity data. Four patients developed severe pancreatitis during PEGasparaginase and two patients during *Erwinia* asparaginase; these patients discontinued asparaginase permanently. No grade 3/4 dyslipidemia was found in patients receiving *Erwinia* asparaginase. However, hypertriglyceridemia and hypercholesterolemia grade 3/4 were found in 47% and 25%, respectively, of the patients treated with PEGasparaginase.

Hyperammonemia grade 3/4 occurred in two patients (9%) treated with *Erwinia* asparaginase, but in none of the patients treated with PEGasparaginase.

Two patients receiving PEGasparaginase and two other

Table 1. Toxicity of PEGasparaginase and *Erwinia* asparaginase.

	PEGasparaginase (n=67)				*Erwinia* asparaginase (n=22)				*P*
	Grades 1/2		Grades 3/4		Grades 1/2		Grades 3/4		
	n	%	n	%	n	%	n	%	
Pancreatitis	0	0	4	6	1	5	2	9	ns
Hypertriglyceridemia	15	22	31	47	7	32	0	0	P<0.001
Hypercholesterolemia	6	9	17	25	8	37	0	0	P=0.01
Hyperammonemia	34	51	0	0	9	41	2	9	ns
Thrombosis*	0	0	2	3	0	0	2	9	ns
Central neurotoxicity	0	0	7	10	0	0	1	5	ns

**not related to vascular access.* P-*values are given for the comparisons of grade 3/4 toxicities between PEGasparaginase* versus Erwinia *asparaginase. ns: not significant.*

patients receiving *Erwinia* asparaginase developed thrombosis. There was no standard policy to evaluate the coagulation pattern during asparaginase therapy and none of the patients received prophylactic treatment. Asparaginase therapy was stopped in these four patients and reintroduced again after 3 or 4 weeks with low molecular weight heparin therapy for at least 3 months and prophylaxis thereafter until finishing asparaginase therapy. No recurrence of thrombosis was seen thereafter.

Central neurotoxicity grade 3/4 occurred in 10% of patients treated with PEGasparaginase and in 5% of those treated with *Erwinia* asparaginase. Central neurotoxicity included somnolence or seizures (grade 3/4) or posterior reversible encephalopathy syndrome.

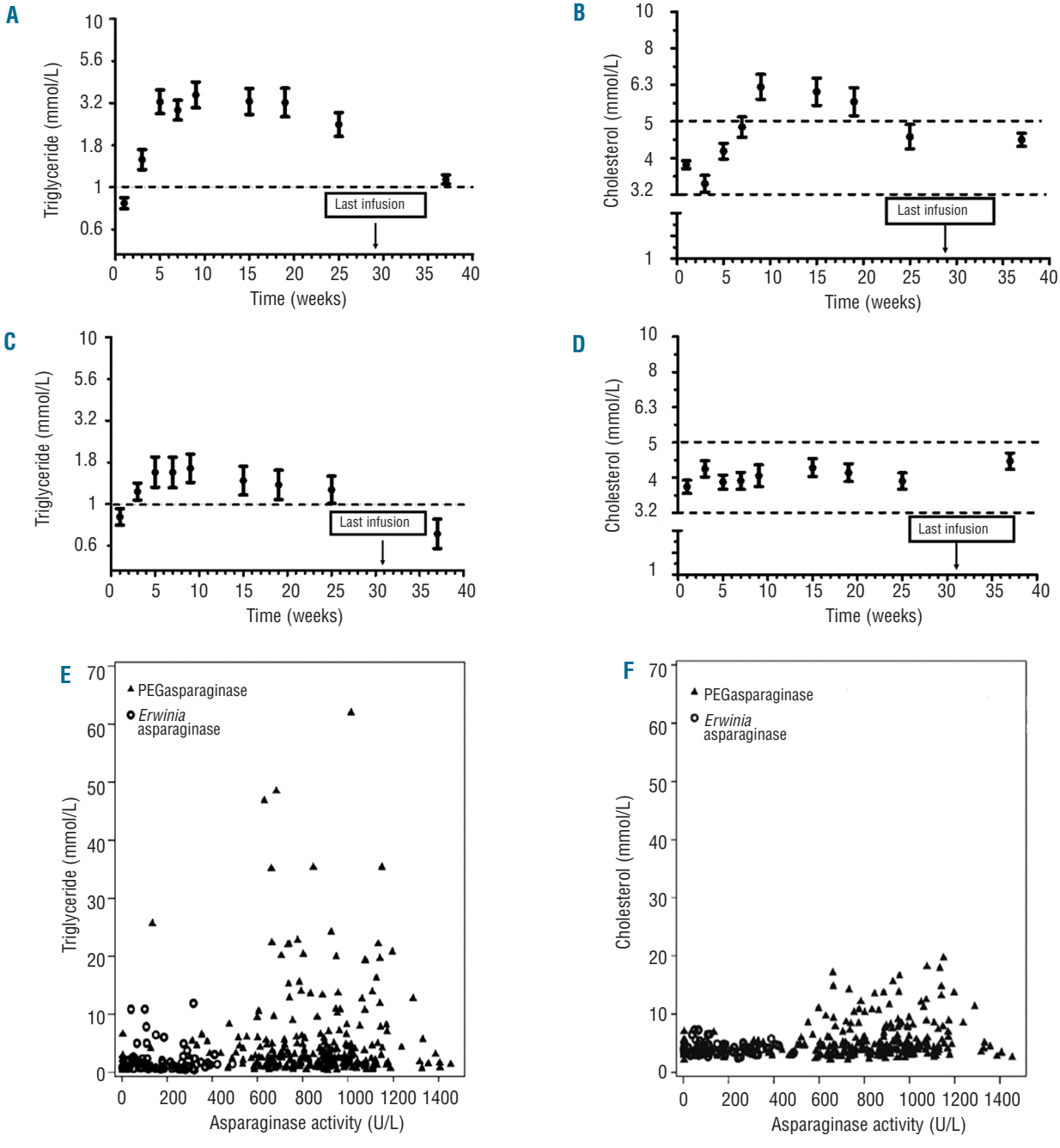

Figure 1. Serum triglyceride, and cholesterol levels over time (mean ± SEM) and relations to serum asparaginase activity. Triglyceride levels (A) and cholesterol levels (B) during PEGasparaginase therapy, triglyceride levels (C) and cholesterol levels (D) during *Erwinia* asparaginase therapy. Mean ± SEM. Association between triglyceride and asparaginase activity (E) and association between cholesterol and asparaginase activity (F). The dotted lines in panels (B) and (D) represent the upper and lower limits of normal. The dotted line in panels (A) and (C) represent the upper limit of normal; as the lower limit of normal is 0 mmol/L this line is not shown.

No difference was found between PEGasparaginase and *Erwinia* asparaginase for any of the grade 3/4 toxicities (pancreatitis, thrombosis, central neurotoxicity) (all $P>0.27$).

Clinical course of dyslipidemia and associations with asparaginase activity

Serum triglyceride and cholesterol levels were measured in 380 samples from 67 children on PEGasparaginase and 140 samples from the remaining children on *Erwinia* asparaginase. In total 460 samples were scheduled for the children on PEGasparaginase, so in 83% of the patients a sample was successfully obtained. In total 161 samples should have been obtained from the children on *Erwinia* asparaginase, leading to a similar percentage of successfully obtained samples.

The median triglyceride level was 0.8 mmol/L (upper limit of normal: 1 mmol/L) and the median cholesterol level was 3.7 mmol/L (upper limit of normal: 5 mmol/L) at the start of therapy intensification. Figure 1A shows that after the first and second PEGasparaginase infusions, at weeks 3 and 5, there was a significant increase in mean triglyceride levels ($P<0.001$). From week 5 until the last PEGasparaginase infusion was given, triglyceride levels remained high and no significant changes were seen. Cholesterol levels increased significantly ($P<0.001$) during the first 9 weeks of PEGasparaginase therapy and remained stable thereafter (Figure 1B). By week 37, the triglyceride and cholesterol levels had normalized in all patients.

The median triglyceride level was 1.3 mmol/L and the median cholesterol level was 4.3 mmol/L at the start of administration of *Erwinia* asparaginase. Figure 1C shows that in the first 2 weeks after starting *Erwinia* asparaginase the triglyceride level increased, but not significantly. Thereafter, the mean triglyceride levels remained stable and normalized by week 37, after the final *Erwinia* asparaginase infusion. Cholesterol levels were within the normal range during and after *Erwinia* asparaginase therapy (Figure 1D).

In one child with extreme hypertriglyceridemia during PEGasparaginase treatment, dexamethasone was temporarily omitted. Another child with extreme hypertriglyceridemia was already successfully managed by temporarily omitting dexamethasone, as described previously.[8] Asparaginase courses were not discontinued in any of the patients with dyslipidemia, and 30 weeks of asparaginase exposure were completed without any other interventions.

It should be noted that the levels of PEGasparaginase activity were much higher than those of *Erwinia* asparaginase activity. Previously, we reported that the trough activity for PEGasparaginase (dose of 2,500 IU/m^2; once every 2 weeks) was 899 U/L and that for *Erwinia* asparaginase (dose of 20,000 IU/m^2; 2-3 times per week) was 157 U/L. Figure 1E,F shows that high triglyceride and cholesterol levels were associated with high levels of asparaginase activity. Studying the correlations between PEGasparaginase activity and triglyceride levels at the various treatment weeks, it was seen that the correlation was strongest at week 5 (Spearman correlation coefficient = 0.36, $P=0.005$). The correlation between PEGasparaginase activity and cholesterol levels was strongest at week 9 (Spearman correlation coefficient = 0.35, $P=0.01$).

Using mixed model analysis, it was found that the triglyceride levels of children ≥10 years old were higher than those of younger patients (<10 years) after adjusting for asparaginase preparations: median 4.9 mmol/L *versus* 1.6 mmol/L ($P<0.001$). The same held true for cholesterol levels, with median values of 6.2 mmol/L *versus* 4.2 mmol/L in the older and younger children, respectively ($P<0.001$).

Clinical course of ammonia levels and toxicities (pancreatitis, thrombosis, central neurotoxicity)

Ammonia levels were measured in 326 samples from 67 children on PEGasparaginase and 102 samples from the remaining children on *Erwinia* asparaginase. In total 460 samples were scheduled for the children on PEGasparaginase, so a sample was successfully obtained from 71% of the patients. In total 161 samples should have been obtained from the children on *Erwinia* asparaginase, leading to a similar percentage of successfully obtained samples.

Figure 2A,B shows the mean ammonia levels during PEGasparaginase or *Erwinia* asparaginase therapy along time. A rapid increase in ammonia levels was observed after the first asparaginase infusions (upper limit of normal: 40 μM). The ammonia levels normalized in all patients by week 37. As far as concerns the incidence of central neurotoxicity, we analyzed the relation with ammonia levels and asparaginase activity using time-dependent Cox regression. We also used Cox regression to analyze the relation of pancreatitis and thrombosis with

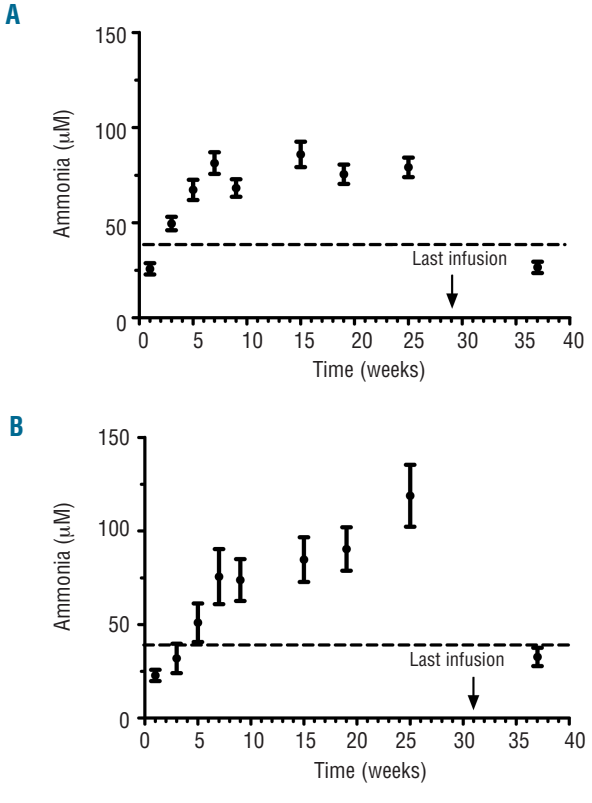

Figure 2. Ammonia levels over time (mean ± SEM) during therapy with (A) PEGasparaginase and (B) *Erwinia* asparaginase (mean ± SEM). The dotted line in panels (A) and (B) represents the upper limit of normal; as the lower limit of normal is 0 μM this line is not shown.

triglyceride levels and asparaginase activity. The results of these analyses are shown in *Online Supplementary Figure S2A-F*. No significant relations were found between levels of asparaginase activity in the serum and the occurrence of pancreatitis, thrombosis or central neurotoxicity or between triglyceride levels and these toxicities.

Discussion

Our study showed that 7% of the patients developed pancreatitis and 4.5% developed thrombosis when receiving very prolonged courses of asparaginases. Recently, the Dana Farber Consortium Institute group reported a comparable incidence of pancreatitis (5%) and thrombosis (8%) with the same schedule.[9] We demonstrate that high levels of asparaginase activity are related to hypertriglyceridemia and hypercholesterolemia (dyslipidemia). It should be noted that PEGasparaginase activity levels were much higher than *Erwinia* asparaginase activity levels. An important observation is that dyslipidemia, even grade 3/4, is temporary and is not associated with clinically relevant events and should not, therefore, be considered a reason for modifying asparaginase treatment. Asparaginase courses were not discontinued in any of the patients with dyslipidemia, and 30 weeks of asparaginase exposure were completed without any other interventions.

Triglyceride levels were increased in patients receiving either PEGasparaginase or *Erwinia* asparaginase, but hypertriglyceridemia was more frequent and more severe during PEGasparaginase treatment. This may be because of the much higher levels of PEGasparaginase compared to *Erwinia* asparaginase. It has been suggested that high triglyceride levels cause severe pancreatitis.[10] However, the highest triglyceride level among the few patients with pancreatitis in our study was only 4 mmol/L (grade 2). Of note, we found the same rate of pancreatitis among patients treated with *Erwinia* asparaginase and none of these patients had hypertriglyceridemia. Furthermore, the asparaginase activity in the patients with pancreatitis was similar to that in the patients without pancreatitis. We, therefore, conclude that the development of pancreatitis is not associated with hypertriglyceridemia or levels of asparaginase activity. In addition, we found that triglyceride levels and asparaginase activity of patients with thrombosis were in the same range as those of patients without thrombosis. This suggests that the development of thrombosis is also independent of the levels of asparaginase activity and triglyceride levels.

Hypertriglyceridemia occurs especially when corticosteroids and asparaginase are combined.[11,12] The decline in triglyceride levels in the two patients in our study who stopped dexamethasone while continuing asparaginase illustrates this.

Temporary hypertriglyceridemia grade 3/4 was seen in about half of the patients receiving PEGasparaginase, although the triglyceride levels normalized completely in all patients after they had finished the 30 weeks of PEGasparaginase infusions. We, therefore, conclude that there is no need to discontinue or interrupt asparaginase therapy in the case of hypertriglyceridemia.

The ammonia levels after *Erwinia* asparaginase therapy were significantly higher than those after PEGasparaginase therapy ($P<0.001$) which seems paradoxical as PEGasparaginase activity was much greater than the *Erwinia* asparaginase activity. However, the difference can be explained by the higher glutaminase activity of *Erwinia* asparaginase, which we recently demonstrated.[6] It has been suggested in case reports that ammonia release could lead to encephalopathy.[13-15] Our prospective study, however, shows that ammonia level was not related to central neurotoxicity. Even the patients with hyperammonemia grade 3/4 did not experience central neurotoxicity and the four patients with central neurotoxicity grade 3/4 did not have higher ammonia levels than those without central neurotoxicity.

The strength of our study was its prospective and longitudinal nature. We closely monitored dyslipidemia and hyperammonemia during very prolonged asparaginase courses in two representative centers in the Netherlands. The limitations lie in the low number of patients experiencing pancreatitis, thrombosis or central neurotoxicity. Particularly, the analyses of patients on *Erwinia* asparaginase with side effects were based on very small numbers (Table 1), so conclusions from these analyses should be interpreted with caution. Larger studies are needed to confirm our conclusions.

In conclusion, this study shows that hypertriglyceridemia and hypercholesterolemia grade 3/4 occur frequently, but are temporary and not associated with clinically relevant events and should not, therefore, be considered a reason for asparaginase treatment modifications. We show that high levels of asparaginase activity are associated with high triglyceride and high cholesterol levels. However, pancreatitis, thrombosis, and central neurotoxicity appear unrelated to asparaginase activity. No associations were found between pancreatitis and hypertriglyceridemia nor between ammonia level and central neurotoxicity.

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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